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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,333	11/14/2003	Anastasia Khvorova	DHARMA 0100-US2	6379
23719	7590	12/11/2006	EXAMINER	
KALOW & SPRINGUT LLP 488 MADISON AVENUE 19TH FLOOR NEW YORK, NY 10022			EPPS FORD, JANET L	
			ART UNIT	PAPER NUMBER
			1633	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/714,333	<b>Applicant(s)</b> KHVOROVA ET AL.	
	<b>Examiner</b> Janet L. Epps-Ford	<b>Art Unit</b> 1633	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 October 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,6,27-29 and 38-60 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6,27-29 and 38-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>2-02-05</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-30-06 has been entered.
2. Claims 1, 6, 27-29, and 38-60 are presently pending.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Response to Arguments***

#### ***Claim Rejections - 35 USC § 112***

4. The rejection of claims 1-6, 8, and 19-37 under 35 USC 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in response to Applicant's amendments.
5. Claims 6, and 27-29 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

Applicant's arguments have been fully considered, but are not persuasive. Applicants traversed the instant rejection on the grounds Applicants have amended the claims to recite limitations that are provided in the specification, including with respect to the recited criteria or variables (see page 16 of 18 in Applicant's response filed 10/30/06). However, contrary to Applicant's assertions, claim 6, and those claims dependent therefrom, claims 27-29, recite the following variable "the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of times that the same nucleotide repeats within a given sequence." These two criteria comprise an exponential number of potential nucleotides, or repeats that can be at particular position within a given siRNA molecule, however the specification as filed does not adequately describe how the full scope of potential combinations of nucleotides variations encompassed by the claims, can be used to design an algorithm for selecting an siRNA molecule.

Other than the following criteria, applicants are not possession of any other sequence structure data that would be useful in designing an algorithm that would select siRNA:

1. A low GC content, preferably between about 30 –52%.
2. At least 2, preferably at least 3 A or U bases at positions 15- 19 of the siRNA on the sense strand.
3. An A base at position 19 of the sense strand.
4. An A base at position 3 of the sense strand.
5. A U base at position 10 of the sense strand.

6. An A base at position 14 of the sense strand.
7. A base other than C at position 19 of the sense strand.
8. A base other than G at position 13 of the sense strand.
9. A T<sub>m</sub>, which refers to the character of the internal repeat that results in inter- or intramolecular structures for one strand of the duplex, that is preferably not stable at greater than 50°C, more preferably not stable at greater than 37°C, even more preferably not stable at greater than 30°C and most preferably not stable at greater than 20°C.
10. A base other than U at position 5 of the sense strand.
11. A base other than A at position 11 of the sense strand.

Due to the ambiguity associated with the disclosure (see pages 26, 40-41 and 53) regarding which particular criteria would yield siRNA according to the present invention, and the apparent need for further experimentation to identify the full scope of non-target specific criteria encompassed by the instant claims, it does not appear that Applicant's were possession of the full scope of variables encompassed by the instant claims, particularly in regards to the generic phrase "the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of times that the same nucleotide repeats within a given sequence."

*New Grounds of rejection:*

6. Claims 43-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite a method for selecting a siRNA for a target gene, wherein said siRNA comprises 19-25 nucleotide base pairs, wherein the method comprises applying the following set of criteria:

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presence of A at position 19 of the sense region, the presence of A at position 3 of the sense region, the presence of U at position 10 of the sense region, the presence of A at position 14 of the sense region, the absence of C at position 19 of the sense region, the absence of G at position 13 of the sense region, the absence of U at position 5 of the sense region and the absence of A at position 11 of the sense region; and

However, it is noted that the instant claims encompass wherein the siRNA comprises 19-25 nucleotides, however according to the specification as filed: "Because according to the present invention a chain can be from 18 to 30 bases in length, and the aforementioned criteria assumes a chain 19 base pairs in length, it is important to keep the aforementioned criteria applicable to the correct bases."

To the extent that the above criteria, specifically the nucleobase positions recited in the above criteria are based upon an siRNA of 19 base pairs in length, it is unclear if assaying for the above nucleotide positions in siRNA molecules of 20-25 base pairs in length would yield an siRNA molecule according to the present invention.

7. Claims 1, 38-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1 and 43 (and those claims dependent therefrom), in step (b) recites "generating **a set** of candidate siRNA molecules," step (c) requires applying a criterion to each of said candidate siRNA molecules, and step (d) comprises "selecting **a** candidate siRNA...if said candidate siRNA satisfies said criterion." The instant claim is vague and indefinite since it is unclear if the **a** candidate siRNA recited in step (d), is selected from among the **set** of candidate siRNA molecules generated in step (b).

***Claim Rejections - 35 USC § 101***

9. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6, 27-29 are drawn to a process. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999))). In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments. In the instant case, the claims are drawn to a method for developing an siRNA algorithm for selecting siRNA. However, the claimed method does not appear to be specific in nature, since the algorithm appears to be generally associated with predicting the internal stability of any duplex RNA. Moreover,

it does not appear that the claimed method produces a concrete or tangible result, as the overall result of the method is directed to the development of an algorithm.

Claims 6, and 27-29 do not produce a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a display or a memory or another computer on a network, or to a user, or by including physical transformation.

***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 6 and 27-29 are rejected under 35 U.S.C. 102(e) as being anticipated by McSwiggen et al. (US 2005/0176025 A1; priority date 7/18/02 to provisional application 60/396905).

12. The instant claims are drawn to a method for developing an siRNA algorithm for selecting siRNA, said method comprises applying one or more, and up to four or more of the following variables selected:

from the group consisting of: the total GC content, melting temperature of the siRNA, GC content at positions 15 -19, the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of times that the same nucleotide repeats within a given sequence ~~and said algorithm~~



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13. McSwiggen et al. teach that an algorithm can be used in a method for ranking or optimizing interfering nucleic acid, by means of applying the following criterion: (see examples 2-3, paragraphs [0387]-[0390])

a) The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.

b) The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.

c) The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.

d) The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.

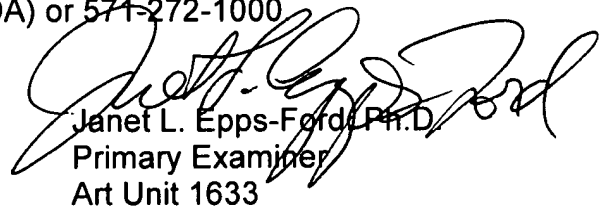
The above criteria of McSwiggen et al. includes at least four criteria that fall within the scope of the claimed invention, thus McSwiggen et al. anticipates the claimed invention.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Janet L. Epps-Ford, Ph.D.  
Primary Examiner  
Art Unit 1633

JLE